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EXAMINER	
NIEBAUER, RONALD T	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,903	GIANNI ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-30 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 2/17/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 1-26,31 have been cancelled.

Claims 27,30,32-36 have been amended.

Claims 27-30,32-36 are under consideration.

Claim Rejections - 35 USC § 103

Claims were previously rejected under 103 using the references cited below. Since the claims have been amended, a new rejection adapted to the claims is recited below using the same references as in the previous rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27-30,32,34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry for neutropenia, as cited previously) and Hattori et al (Nature Medicine v8 2002 pages 841-849 as cited previously).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells for use in transplantation in particular autologous or allogenic transplantation and to treat neutropenia for example. Robinson does not define neutropenia. The Merck Manual (accessed from http://www.merck.com/mmhe entry for neutropenia) teaches that neutropenia is an abnormally low number of neutrophils in the blood (first sentence). The Merck Manual teach that neutrophils are white blood cells (page 1 9th sentence). Thus, Robinson motivates treating those with a low number of neutrophils in the blood as in claim 30. The Merck Manual is cited to show a universal fact and definition and as such the date of the reference is not relevant (see MPEP section 2124). Further, since Robinson specifically teach the use for autologous or allogenic transplantation, Robinson motivate the patient population as recited in claim 30 and dependent claims. Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Robinson teach (page 535 2nd column see also titles of reference 2) that G-CSF has been used in the clinic following chemotherapy thus meeting the patient population recited in claim 30 of the instant invention. Robinson teach (page 535 2nd

column see also titles of references 5-7 on page 538) that G-CSF was administered to improve neutrophil recovery and significantly reduced the period of neutropenia.

Robinson does not expressly teach the use of G-CSF together with the use of placental growth factor.

Robinson recognize that rapid clearance is a disadvantage of recombinant molecules and that a goal is to achieve clinical efficacy with fewer injections (abstract). Robinson recognize optimization of administration (page 537 'summary' section). Thus one would be motivated to look for alternate strategies and techniques to achieve such a goal.

Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4). Hattori teach that the studies suggest that PlGF which is endowed with a low toxicity profile provides a strategy to induce hematopoiesis after chemotherapy/radiation (compare claim 30 of the instant invention), or in hematological disorders (page 842 first paragraph).

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. As such, the prior art included both elements of the instantly claimed compositions: G-CSF and PlGF. One of skill in the art could have combined the elements as claimed by known methods with no change in their respective function (mobilize hematopoietic stem cells) and the combination would have yielded predictable results to one of ordinary skill in

the art at the time of the invention. Since Hattori teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4) and Robinson teach that G-CSF is widely used (abstract) one would have a reasonable expectation of success.

Further, section 2144.06 of the MPEP states that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition. The idea of combining them logically flows from their having been individually taught in the prior art. Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells. The work of Hattori (page 844 last paragraph to page 845 first paragraph and figure 4) suggest that placental growth factor mobilize hematopoietic stem cells. Therefore, the combination of G-CSF and PlGF to mobilize hematopoietic stem cells logically flows from their having been individually taught in the prior art.

Robinson teach (abstract) the use of recombinant human granulocyte colony stimulating factor (G-CSF) as recited in claim 27. Although Hattori does not expressly teach the use of the recombinant human PlGF it would have been obvious to use a recombinant and human version of the molecule since such substitutions are well-known in the art. The substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. As such, the limitations of claim 28 are met.

Since Robinson teach that the G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF combination in such forms, for ease of administration for example, thus meeting the limitations recited in claim 29. It is noted that claim 27 for example, allows the inclusion of excipients.

Further, it would have been obvious to administer the G-CSF and PlGF either separately in sequence or simultaneously since those are the typical well-known modes of administering combinations thus meeting the limitations recited in claims 32,34-36 of the instant invention. Further, since Robinson (page 535 2nd column) recognize the use of daily injections one would be motivated to use daily administrations as recited in claim 36.

It is noted that claim 27 states 'wherein said composition is able to….'. Since the combination of Robinson and Hattori teach the combination recited in the instant claims the properties recited in the claims are necessarily present absence evidence to the contrary (see MPEP section 2112.01).

It is noted that claim 35 recites 'consisting essentially of'. Section 2111.03 of the MPEP states:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention.
> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising."

In the instant case, there is no clear indication in the specification or claims as to what the basic and novel characteristics are. Therefore, "consisting essentially of" will be construed as equivalent to "comprising" in claim 35.

Claims 27-30,32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al (In vivo v16 2002 pages 535-540 as cited previously) and Merck Manual (entry for neutropenia, as cited previously) and Hattori et al (Nature Medicine v8 2002 pages 841-849

as cited previously) and Anderlini et al (Journal of the American Society of Hematology v90 1997 page 903-908 as cited previoulsy) and Carmeliet (US 7,105,168 as cited previously).

As discussed above, Robinson, Merck Manual, and Hattori render obvious claims 27-30,32,34-36.

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g.doses), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

Anderlini teach that doses of, for example, 24 ug/kg/day (page 904 first column 16th line from the bottom) of recombinant human G-CSF have been used previously thus meeting the range as recited in claim 33 of the instant invention. Carmeliet teach PlGF (specifically human PlGF column 6 line 9) use as part of treatments such as for transplantations (column 3 line 22) and specifically teach that recombinant PlGF is used (column 15 line 7) and PlGF dosages 'of 15ug/kg/day of active ingredient up to 100 ug/kg/day or higher' (column 15 line 12) are deemed to be a safe level thus meeting the range as recited in claim 33 of the instant invention. Although the references do not necessarily teach G-CSF and PlGF for the identical use as in the instant invention, one of skill in the art would use the prior art doses as starting points for the routine optimization.

Response to Arguments 103 rejection

Since the claims have been amended, a new rejection adapted to the claims is recited above using the same references as in the previous rejection. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that one of skill in the art would not have a reasonable expectation of success that the combination would provide increased mobilization of blood cells. Applicants argue that Robinson teach that GCSF results in fluctuations and that Robinson teach a goal of clinical efficacy with fewer injections. Applicants argue that one would be inclined to use a treated protein, continuous infusion or adenovirus vector.

Applicants argue that Hattori teaching of an adenovirus expressing PlGF is not predictive of administration of PlGF. Applicants argue that the instant specification warns that an adenovirus might not be predictive of direct injection. Applicants argue that when Figure 4c of Hattori is compare to the instant invention that differences can be seen.

Applicants argue that one would not have been able to predict the synergistic activity and the unexpected result is evidence of unobviousness. Applicants argue that example 2 of the specification shows a 1.5 fold increase. Applicants point out that rhPlGF is decidedly more powerful than rmPlGF. Applicants conclude that there is a huge difference between administration of an adenovirus and a purified protein.

Applicant's arguments filed 2/17/09 have been fully considered but they are not persuasive.

Although Applicants argue that one of skill in the art would not have a reasonable expectation of success for the combination, Robinson teach that G-CSF is widely used to

mobilize stem cells (abstract). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and that PlGF provides a novel strategy for use after chemotherapy (page 842 first column). Thus, the prior art teach positive results for each of the components. Although applicants argue that Robinson teach fluctuations, Robinson expressly states that the protein can be administered 'to achieve biological efficacy' (page 537 section 'summary'). Since biological efficacy can be achieved one would recognize that G-CSF administration is desirable and can be used with a reasonable expectation of success. Although Applicants argue that one would be inclined to use a treated protein, continuous infusion or adenovirus vector, it is noted that the instant rejection is a multiple reference 103 rejection. As such, a single reference does not teach all of the claim limitations. Since Robinson teach that the G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF combination in such forms, for ease of administration for example. It is noted that section 2141 of the MPEP states:

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton."KSR, 550 U.S. at ___, 82 USPQ2d at 1397. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ."Id. at ___, 82 USPQ2d at 1396.

In the instant case, although Hattori teach the use of an adenovirus one of skill in the art would not be limited to use of an adenovirus as a method of delivering a protein. Since Robinson teach

that G-CSF can be administered by infusion or injection (abstract, page 535 2nd column) one would be motivated to formulate the G-CSF and PlGF combination in such forms, for ease of administration for example. In other words, one would be motivated to standardize the mode of administration so that the G-CSF and PlGF could be co-administered. One of skill in the art would recognize that the active protein ingredient that is expressed via the adenovirus (i.e. PlGF) is an active protein ingredient like that which is delivered directly via injection of a protein for example (i.e. PlGF).

Although Applicants argue that Hattori teaching of an adenovirus expressing PlGF is not predictive of administration of PlGF, it is first noted that section 2143.02 of the MPEP states: "Obviousness does not require absolute predictability, however, at least some degree of predictability is required." In the instant case, one of skill in the art would recognize that the active protein ingredient that is expressed via the adenovirus (i.e. PlGF) is an active protein ingredient like that which is delivered directly via injection of a protein for example (i.e. PlGF). Although the applicants try to make comparisons between the instant specification and the prior art, it is noted that numerous variables are different in the experiments which could account for any differences. Further although applicants argue that the specification warns that an adenovirus might not be predictive of direct injection, it is noted that section 2145 of the MPEP states: "An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness." In the instant case, applicants refer to differences in which a mouse PlGF is used (example 2 of specification) and then go on to say (page 9 of reply 2/17/09) that the mouse and human PlGF behave somewhat differently. Further, the example of Hattori involves intravaneous injection

while example 2 of the specification involves intraperitoneal injection. As such, there are numerous possible reasons for experimental variability. Rergardless of the experimental differences, since Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and that PlGF provides a novel strategy for use after chemotherapy (page 842 first column) one would have a reasonable expectation of success when PlGF is administered via any standard method.

Although Applicants argue that one would not have been able to predict the synergistic activity and the unexpected result is evidence of unobviousness, section 716.02(a) of the MPEP states:

However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

In the instant case, Robinson teach that G-CSF is widely used to mobilize stem cells, for example (abstract). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and that PlGF provides a novel strategy for use after chemotherapy (page 842 first column). Thus, the prior art teach positive results for each of the components. Further, Hattori

teach that PlGF augmented the number of pluripotent hematopoietic cells by 20-fold (page 845 first column and Figure 4). As such, one would expect an increase when using PlGF. Since Hattori teach 20-fold increases, the 1.5fold increases are not deemed unexpected, even if one accepted that increases might vary based on the mode of administration. In the instant case, the teachings of the prior art lead to a general expectation of increases when PlGF is used.

Conclusion

Claims were previously rejected under 103 using the references cited above. Since the claims have been amended, a new rejection adapted to the claims is recited above using the same references as in the previous rejection.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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